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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,111	03/10/2004	Dario Norberto R. Carrara	88066-7900	5916

28765 7590 05/20/2010

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EXAMINER	
SCHLIENTZ, NATHAN W	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
05/20/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/798,111	CARRARA ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,13,15-27,29-31,37,40-47 and 56-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13,15-27,29-31,37,40-47 and 56-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1, 3-11, 13, 15-27, 29-31, 37, 40-47 and 56-68 are pending and will presently be examined on the merits for patentability. No claim is allowed at this time.

Withdrawn Rejections

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1, 3-11, 13, 15-27, 29-31, 37, 40-47 and 56-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims recite or depend from a claim that recites "between about" in references to concentration ranges, "from about"... "to about" in reference to effective dosage amounts, and "to about" in reference to serum levels. However, "between", "from... to", and "to..." implies a specific range with definite end values, whereas "about"

encompasses other values close to the end values. Therefore, the scopes of the ranges are not clearly defined.

Response to Arguments

Applicants argue on page 13 that the phrases recited in the present claims, i.e., "between about", "from about" ... "to about", and "to about" are specific and definite. Applicants further point to the MPEP for support that the term about doesn't automatically render the claim indefinite. However, claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits". The examiner respectfully argues that the instantly claimed ranges are variable and one of ordinary skill in the art would not be apprised of what values fall within the scope of the instant ranges. The term 'about' gives no hint as to which value constitutes infringement. Nothing in the specification, prosecution history, or prior art provides any indication as to what range of values is covered by the term "about". For instance, it is not clear if 16%, 17%, 18%... by weight of polyalcohol and permeation enhancer are within or outside the scope of instant claim 1. The recitation of a range implies a beginning and end to the range, but the term "about" encompasses values that are within a certain proximity of the value. Therefore, it is not clear where the ranges begin and end.

2. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 27 is dependent from claim 13, which is dependent

from claim 1. Claim 1 recites that *when the active agent is testosterone it is the sole active agent* and is present at 1% or less by weight of the formulation. However, claim 27 recites that the active agent is testosterone *in combination with a further active agent* selected from the group consisting of estrone, estradiol, 17 estradiol, ethynil estradiol, estriol succinate, estriol dihexanate, and estriol sulfamate. It is unclear how in claim 27 the active agent can be testosterone in combination with another active agent when claim 1 clearly states that if the active is testosterone it is the sole active agent. For the purposes of search and examination, claim 27 is construed as if the sole active agent is testosterone present at 1% or less by weight, which is consistent with claim 1. Therefore, claim 27 is not being searched for a combination of testosterone and another active agent hormone selected from the group consisting of estrone, estradiol, 17 estradiol, ethynil estradiol, estriol succinate, estriol dihexanate, and estriol sulfamate.

3. Claims 60 and 66-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 60 recites the limitation "the polyalcohol" in the 15th line. There is insufficient antecedent basis for this limitation in the claim. It is believed applicants intended to state "the propylene glycol".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 60 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Carrara et al. (WO 02/11768 A1).

Carrara et al. disclose a composition comprising 1.25 wt.% testosterone, 5.00 wt.% diethylene glycol monoethyl ether (Transcutol P), 5.95 wt.% propylene glycol, 43.09 wt.% ethyl alcohol, 43.07 wt.% water, 1.20 wt.% carbomer (Carbopol 980 NF, a gelling agent), 0.38 wt.% triethanolamine (a neutralizing agent), and 0.059 wt.% disodium EDTA (a sequestering agent) (Example 2).

Response to Arguments

Applicant's Remarks on page 14 have been fully considered but they are not persuasive. Applicants argue that they amended claims 1 and 37 to recite that when the active agent is testosterone, it is the sole active agent and is present at 1% or less by weight of the formulation. However, applicants did not amend claim 60 to comprise this limitation. Therefore, claims 60 and 68 allow for any amount of testosterone.

2. Claims 1, 3-8, 10, 11, 13, 15, 20, 22, 37, 40-43, 45-47, 56, 57, 60-62 and 68 are rejected under 35 U.S.C. 102(a) as being anticipated by Gray et al. (WO 02/22132; US 7,030,104 is the English-language equivalent and is relied upon herein).

Gray et al. disclose in Table 1 gel formulations (Reference G29-287, G29-299 and Tx11323) for percutaneous administration wherein the gels comprise:

REFERENCE	G29-287	G29-299	Tx11323 batch-12
NAc (nomegestrol acetate)	0.4	0.4	—
Estradiol	—	0.1	0.1
Carbopol 1342 or 1382	0.5	0.5	0.5
Propyleneglycol	6	6	6
Transcutol	5	5	5
Solketal			
EDTA	0.05	0.05	0.05
Triethanolamine	0.3	0.3	0.3
Demineralized water	42.75	42.65	43.05
95° Ethanol	45	45	45

Gray et al. also disclose topically administering two gel formulations A and B (Table 5), depicted below, to women by spreading 3 g of gel per day over 400 cm^2 (col. 13, ln. 1-25).

TABLE 5

formula of the 2 gels used for pharmacokinetic trials in women

	Gel A	Gel B
Nomegestrol acetate	0.40	0.40
Propylene glycol	8.00	8.00
Solketal	3.00	3.00
Carbopol 980	0.60	
Carbopol 1382		0.50
EDTA	0.05	0.05
TEA	0.24	0.30
95° Ethanol	45.00	45.00
Demineralized water	42.69	42.73

Gray et al. further disclose that topically administering gel TX11323 (shown above) at a rate of 3 g of gel on a body area of 400 cm^2 leads to plasmatic levels of estradiol at the equilibrium of approximately 40 pg/ml, which are located in the area of effective plasmatic concentrations of estradiol as these are comprised between 30 and 60 ng/ml (col. 14, ln. 1-6). Gray et al. disclose that estradiol gels likely to produce satisfactory clinical results must present during in vitro tests of percutaneous passage cumulative quantities of estradiol at 24 hours of greater than 1.05 µg without exceeding 2.1 µg so as not to induce hyperestrogenosis (col. 14, ln. 7-15).

Therefore, Gray et al. disclose a gel comprising:

- a hormone (nomegestrol acetate, a progestin, at 0.4 wt.% (G29-287); estradiol, an estrogen, at 0.1 wt.% (Tx11323 batch-12); or a combination thereof (G29-299));
- a gelling agent (Carbopol 1342 or 1382) at 0.5 wt.%;
- an alkanol (95° ethanol) at 45 wt.%;
- a polyalcohol (propylene glycol) at 6 wt.%;
- a permeation enhancer (Transcutol® (diethylene glycol monoethyl ether), or Solketal) at 5 wt.%;
- a neutralizing agent (triethanolamine) at 0.3 wt.%;
- a sequestering agent (EDTA) at 0.05 wt.%; and
- water at 42.65-43.05 wt.%.

Gray et al. disclose administering the gels to women for to determine the pharmacokinetic behavior or percutaneous administration for hormonal treatment of perimenopause and menopause as well as ovarian hormonal deficiencies (col. 1, ln. 15-19; col. 2, ln. 12-16; and col. 14, ln. 1-15).

Response to Arguments

Applicants argue on page 14 that Gray et al. do not disclose a formulation comprising a hormone, provided that when the hormone is estrogen, progestin is not

present in a therapeutically effective amount, when the hormone is progestin, estrogen is not present in a therapeutically effective amount, and when the hormone is testosterone it is the sole active agent and is present at 1% or less by weight of the formulation. However, as discussed above, Gray et al. clearly disclose compositions comprising nomegestrol acetate without a therapeutically effective amount of estrogen (G29-287 in Table 1; and Gels A and B in Table 5), and estradiol without a therapeutically effective amount of progestin (Tx11323 in Table 1). Therefore, Gray et al. clearly anticipate the instant claims.

3. Claims 1, 3-8, 10, 11, 13, 15, 20, 22, 37, 40-43, 45-47, 56, 57, 60-62 and 68 and 68 are rejected under 35 U.S.C. 102(e) as being anticipated by Gray et al. (US 7,030,104 and US 2003/0181430) for the same reasons as above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1, 3-11, 13, 15-27, 29-31, 37, 40-47 and 56-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (WO 02/22132; US 7,030,104; and US 2003/0181430), in view of Dudley et al. (US 6,503,894), Labrie (US 5,955,455), Catherino et al. (J. Steroid Biochem. Molec. Biol., 1995) and Wang et al. (The Journal of Clinical Endocrinology and Metabolism, 2000).

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Gray et al. are discussed above and incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

With regard to instant claims 23-25, Gray et al. do not specifically recite that the free serum concentration of estradiol is increased to about 8.8 ng/dl, nor increases in serum levels of estrone to about 10.4 ng/dl or 193 ng/dl. However, Gray et al. teach that topically administering gel TX11323 (estradiol gel) at a rate of 3 g of gel on a body area of 400 cm^2 leads to plasmatic levels of estradiol at the equilibrium of approximately 40 pg/ml, which are located in the area of effective plasmatic concentrations of estradiol as these are comprised between 30 and 60 ng/ml (col. 14, ln. 1-6). Gray et al. teach that estradiol gels likely to produce satisfactory clinical results must present during in vitro tests of percutaneous passage cumulative quantities of estradiol at 24 hours of

greater than 1.05 µg without exceeding 2.1 µg so as not to induce hyperestrogenosis (col. 14, ln. 7-15). Therefore, it would have been well within the purview of one of ordinary skill in the art to administer enough estradiol gel according to Gray et al. in order to achieve desired free serum concentrations of estradiol as well as serum level increases of estrone.

With regard to instant claims 9, 16-19, 21, 26, 27, 29, 30, 44 and 64-67, Gray et al. do not teach their topical hormonal compositions to comprise an androgen or a progestin as listed in claim 21. However, Dudley et al. teach topical formulations for treating hypogonadism in males comprising androgenic steroids or progestogens (col. 11, ln. 63 to col. 12, ln. 1; and Table 5). Dudley et al. teach that the composition comprises an androgenic steroid, such as testosterone, methyltestosterone and/or methandrostenolone (col. 11, ln. 63 to col. 12, ln. 1), or a progestogen, such as anagestone, chlormadinone acetate, delmadinone acetate, etc. (col. 12, ln. 2-13); a C1-C4 alcohol, such as ethanol (col. 12, ln. 17-18); a penetration enhancer, such as diethylene glycol monoethyl ether (col. 12, ln. 54-55); a thickener, such as Carbopol (col. 12, ln. 60-67); and water (col. 12, ln. 17-22). Dudley teaches a testosterone gel named AndroGel® that comprises 1 wt.% testosterone (Table 5). Therefore, it would have been well within the purview of one of ordinary skill in the art to use the appropriate hormones, such as testosterone at 1 wt.%, methyltestosterone and methandrostenolone, or a progestogen, in the formulations of Gray et al. for treating a person for hypogonadism. Also, Catherino et al. teach that megestrol acetate and nomegestrol acetate differ only at the 19 position, and that nomegestrol is a clinically

useful progestin and an effective contraceptive agent when used as an implant (pg. 239, right column, ln. 3-7; and pg. 243, left column, last line to right column, ln. 7). Thus, it would have been obvious for one of ordinary skill to substitute megestrol acetate in the place of nomegestrol acetate, as they differ only in the absence of a methyl at the 19 position and are both useful progestins.

With regard to instant claims 31 and 59, Labrie teaches that dehydroepiandrosterone (DHEA) is useful for the treatment of hypogonadism and conditions related to decreased secretion of sex steroid precursors by the adrenals (Abstract). Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art to use DHEA in the formulations of Gray et al. in order to treat hypogonadism.

With regard to instant claims 58 and 63, Gray et al. do not teach a kit comprising a container that retains their compositions and includes a pump for dispensing a predetermined dosage or volume of the formulation upon demand. However, delivering hormone gels via actuation of a pump is readily known in the art, as shown by Wang et al. wherein hydroalcoholic gels containing 1 wt.% testosterone were packaged in multidose bottles with an actuator pump for treatment of hypogonadal males (pg. 2840, right column, "T gel and patch").

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to treat hypogonadism with the compositions of Gray et al., using as the androgen testosterone, methyltestosterone, methandrostenolone,

DHEA or combinations thereof, and as the penetration enhancer diethylene glycol monoethyl ether, as reasonably taught by Dudley et al. and Labrie et al. Further, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to package the hydroalcoholic gels into multidose bottles with an actuator pump for dispensing predetermined dosages, as reasonably taught by Wang et al.

With regard to the combination of methyltestosterone and methandrostenolone, such would have been obvious in the absence of evidence to the contrary because it is generally prima facie obvious to use in combination two or more ingredients that have previously been used separately for the same purpose to form a third composition useful for that same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. *In re Kerkhoven* 626 F.2d 646, 850, 205 USPQ 1069, 1072 (CCPA 1980).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants argue on page 15 that the various references that have been combined in the office action are not related and do not teach that they should be combined as suggested. However, the examiner respectfully argues that the references are all within the same field of endeavor, topical application of hormones. Therefore,

one of ordinary skill in the art would look to other teachings within the same field of endeavor. Also, one of ordinary skill in the art would have a reasonable expectation of success in using the topical formulations of Gray et al. to administer other hormones since Dudley et al. teach their compositions to comprise the same components for topical application (active, gelling agent/thickener, alcohol, penetration enhancer, and water). Thus, one of ordinary skill in the art would reasonably expect to be able to treat other conditions, such as hypogonadism, with hormones known for their treatment, formulated into the topical gel formulations according to Gray et al.

Applicants further argue that one would have to selectively pick and choose from various combinations of ingredients using the present specification as a guide in order to achieve the instant invention. However, the examiner respectfully argues that hormone therapy is well-known in the art. One of ordinary skill in the art would know what hormones are effective for treating various conditions, without looking to the instant specification. Gray et al. teach a carrier that is sufficient for administering estradiol to patients for hormonal treatment of perimenopause and of menopause as well as treatment of ovarian hormonal deficiencies in women with amenorrhea. Dudley et al. teach a very similar carrier (active, gelling agent/thickener, alcohol, penetration enhancer, and water) as suitable for administering androgens and progestogens for treatment of hypogonadism. Therefore, one of ordinary skill in the art would not need the instant specification to prepare gel formulations according to Gray et al. wherein the hormone is an androgen, progestogen and estrogen. One of ordinary skill in the art would have a reasonable expectation of success in using androgens, estrogens and

progestogens in formulations according to Gray et al. which comprise a gelling agent, alcohol, polyalcohol, and permeation enhancer.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616